EXHIBIT 8

Original Reports | Cancer Prevention and Control

Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis

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ABSTRACT

PURPOSE Intimate care products may contain substances associated with increased risk of hormone-related cancers. The relationship between genital talc use and ovarian cancer, in particular, has been well studied, but concerns about recall bias and exposure misclassification have precluded conclusions. We examined the association between intimate care products and female hormone−related cancers, accounting for potential biases, using data from a US-based cohort study.

METHODS The Sister Study enrolled 50,884 women who had a sister with breast cancer. Data on genital talc use and douching were collected at enrollment (2003-2009) and follow-up (2017-2019). We used Cox proportional hazards models to estimate hazard ratios (HRs) for associations between intimate care product use and breast, ovarian, and uterine cancers. To account for potential exposure misclassification and recall bias, we conducted quantitative bias analyses under various exposure reassignment assumptions.

RESULTS Across considered scenarios, 41%-64% of participants douched and 35%-56% used genital talc. In models adjusted for exposure misclassification, genital talc use was positively associated with ovarian cancer (HR range, 1.17-3.34) Frequent douching and douching during young adulthood were positively associated with ovarian cancer, but neither douching nor talc was associated with breast or uterine cancer. Differential reporting of talc use by cases and noncases likely produces positive biases, but correcting for error still resulted in HRs above 1.0. For example, HR, 1.40 (95% CI, 1.04 to 1.89) when 25% of exposed cases and 10% of unexposed noncases had talc status reassigned.

CONCLUSION Although results show how differential recall would upwardly bias estimates, corrected results support a positive association between use of intimate care products, including genital talc, and ovarian cancer.

INTRODUCTION

Intimate care products may contain endocrine-disrupting chemicals, such as phthalates, parabens, and bisphenols,[1,2] which can alter endogenous hormone levels and potentially affect the risk of developing hormone-related diseases such as breast, ovarian, or uterine cancer. They may also contain other known or suspected carcinogens such as volatile organic compounds[3,4] and asbestos.[5,6]

Douche and powder are two commonly used intimate care products. Douches are liquids inserted into the vagina using a device that produces an upward stream. Initially promoted as contraception,[7] women also douche to improve perceived cleanliness and reduce odor, particularly after sexual intercourse or menstruation.[8] Although some douches contain only water or vinegar, endocrine-disrupting chemicals and

volatile organic compounds have been detected in commercially available products,[2,4] and users have elevated urinary phthalate levels.[9] Douching has been linked to adverse reproductive health outcomes, including pelvic inflammatory disease, bacterial vaginosis, and ectopic pregnancy.[10] It is also considered a risk factor for cervical cancer[10,11] and possibly ovarian cancer.[12,13]

Powder consisting of talc or cornstarch may be applied to the genital area to prevent dampness and chafing, promote a feeling of cleanliness, or reduce odor.[8] Genital powder use became a public health concern because of the natural co-occurrence of talc and asbestos.[6] Although recent surveillance identified asbestos particles in certain talc products,[5] the prevalence of asbestos contamination is unknown, given the lack of routine monitoring. Use of powder in the genital area could plausibly promote carcinogenesis through

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CONTEXT

Key Objective
Are history of genital talc use and douching associated with breast, ovarian, or uterine cancer after correcting for likely biases?

Knowledge Generated
Genital talc use was positively associated with ovarian cancer for a range of plausible bias-correction scenarios, with higher rates seen for frequent and long-term users. Douching frequently and during young adulthood were also positively associated with ovarian cancer, but neither douching nor talc was associated with breast or uterine cancer.

Relevance *(G. Fleming)*
These findings support the hypothesis that there is a positive association between genital talc use and development of ovarian cancer, but unmeasured confounding could still be present.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

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mechanisms other than direct contact with asbestos, including exposure to other chemicals[1,3] or irritation and inflammation of the reproductive tract.

When considering the potential carcinogenicity of intimate care products, the relationship between genital powder use and ovarian cancer has been especially well studied, although without clear consensus.[14] Initial case–control studies[15-18] indicated a strong positive association that was not replicated in prospective studies,[12,19,20] even when pooled.[21] In studies with retrospective data collection, women with and without ovarian cancer may differentially report exposure, leading to recall bias.[22,23] Although not affected by recall bias, prospective studies tend to have small case numbers and simplified exposure assessments, resulting in low statistical precision and increased likelihood of nondifferential exposure misclassification.

Our main objective was to re-evaluate the associations between intimate care product use and incidence of hormone-related cancers, expanding on previous analyses,[12,24] by incorporating newly diagnosed ovarian and uterine cancers, adding breast cancer as an outcome, and integrating new data on lifetime use of douche and genital talc. Because the newly acquired exposure data were susceptible to differential missingness by cancer status, we used quantitative bias analysis to estimate effects under several missingness assumptions. When examining the association between genital talc use and ovarian cancer, we additionally evaluated the potential impact of recall bias.

METHODS

Study Sample

The Sister Study consists of 50,884 women age 35-74 years who had a sister previously diagnosed with breast cancer, but who did not have breast cancer themselves at enrollment (2003-2009). All resided in the United States and provided written informed consent. The Sister Study is overseen by the institutional review board of the National Institutes of Health.

Participants completed an extensive computer-assisted telephone interview at enrollment, plus a separate personal and intimate care product use questionnaire.[25] Trained examiners took anthropometric measurements. Major health events are reported annually, with extensive follow-up questionnaires completed every 3 years.

We excluded five women who withdrew their consent and 79 with prebaseline breast cancer or unknown status (Fig 1). An additional 994 women were excluded from multivariable analyses because of missing data for key covariates, leaving 49,806. For ovarian cancer analyses, we additionally excluded 225 women with uncertain status or prebaseline ovarian cancer and 8,753 women with previous bilateral oophorectomies. For uterine cancer analyses, we excluded 416 women with uncertain status or prebaseline uterine cancer, as well as 15,202 women with previous hysterectomies. We did not exclude individuals missing data on intimate care product use.

Exposure Assessment

The initial personal care product questionnaire focused on two specific time periods: age 10-13 years and the 12 months before enrollment. Women were asked how frequently they douched and how frequently they "applied talcum powder to a sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area." Participants responded whether they never, sometimes, or frequently used at age 10-13 years, and whether they used never, <1 time/month, 1-3 times/month, 1-5 times/week, or >5 times/week

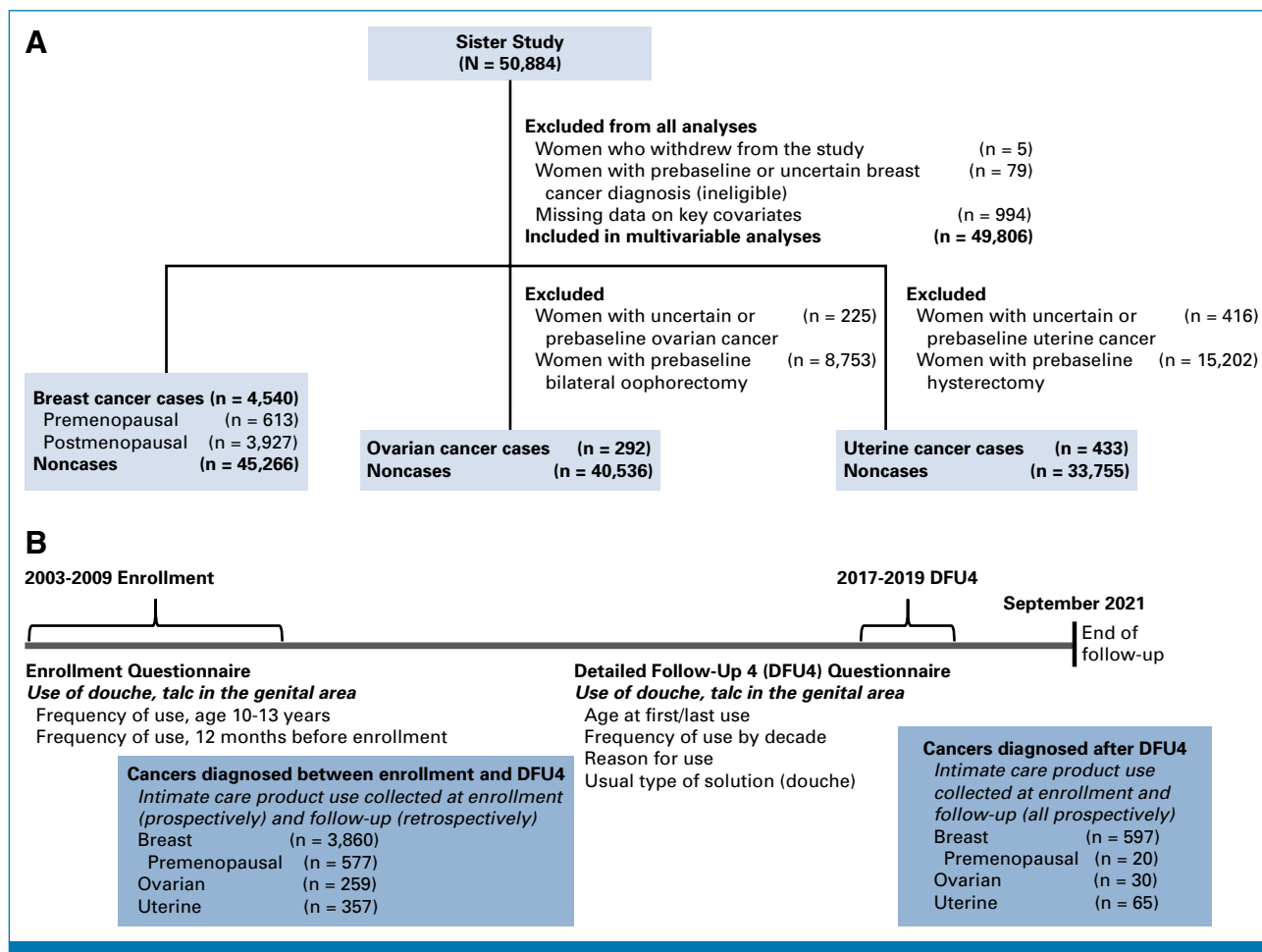Intimate Care Products and Hormone-Related Cancers

FIG 1. (A) Flowchart and (B) timeline describing characteristics and questionnaire data from Sister Study participants included in the quantitative bias analysis of intimate care product use and incidence of female hormone−related cancers.

in the year before enrollment. We considered frequent use to be at least once per month.

More detailed information about use of douche and genital talc was obtained in the fourth follow-up questionnaire (2017-2019). Participants were asked if they ever used the products, and if yes, their age at first and most recent use, and their frequency of use during each decade. We primarily focused on ever versus never use of each product before enrollment, but we also examined frequency, duration, and timing of use.

Data on intimate care product use were sometimes contradictory or missing. Women who provided contradictory reports about intimate care product use in the year before enrollment[8] were initially categorized on the basis of their enrollment report, but we also considered models where a randomly selected subset was reclassified (details in Appendix 1, online only). We also used quantitative bias analyses to implement different approaches for imputing exposure in women who initially reported never use but did not complete the follow-up questionnaire. These comparisons were crucial for understanding potential biases, as women with incident cancer were overrepresented in this undefined group.

Outcomes

Incident cases were women who self-reported cancer of the breast, ovary (including fallopian tubes or peritoneum[26]), or uterus after enrollment. These were verified via medical reports, when possible, with some fatal cases confirmed through the National Death Index or death certificates. Data are complete through September 2021 (data release 11.1).

For most breast cancer analyses, we analyzed pre- and postmenopausal person-time separately to account for differential associations with BMI.[27,28] We additionally examined subtype-specific associations on the basis of estrogen receptor status. We separately assessed medically confirmed serous[29] and nonserous ovarian cancer and medically confirmed endometrial cancers (type 1 or 2).[30]

Covariates

The following covariates were considered potential confounders on the basis of their previously established relationships with intimate care products and hormone-related cancers (all self-reported at enrollment, unless otherwise

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specified): race/ethnicity, attained education, examiner-measured BMI, BMI age 30-39 years, age at menarche, duration of hormonal birth control use, parity, menopausal status, hormone therapy use, geographic region of residence, smoking status, and alcohol use. Other covariates included in imputation models because of possible associations with intimate care product use were childhood household income level, adult household income, highest attained education level in the household when the participant was age 13 years, marital status, and weight relative to peers in teen years.

Statistical Analysis

We first compared covariate distributions across categories of intimate care product use. After excluding women missing key covariates and imputing missing exposure, we used multivariable Cox proportional hazards models with age as the time scale to estimate hazard ratios (HRs) and 95% CIs, adjusting for potential confounders. Follow-up began at enrollment and continued until age at diagnosis, with censoring at the end of follow-up (September 2021), loss to follow-up, or death. For assessments of ovarian and uterine cancers, women were censored at the age of bilateral oophorectomy or hysterectomy, respectively.

In addition to estimating HRs for ever versus never use, we considered the effects of frequent use, long-term use, and use during specific age periods (teens, 20s, 30s, and 12 months before enrollment). Subtype-specific analyses were limited to comparisons of ever versus never use.

We separately estimated HRs for ever versus never use based only on product use as reported at enrollment (prospective) or follow-up (retrospective). Additionally, we considered any product use before the fourth detailed follow-up in relation to cancers occurring after that time (prospective with left truncation). Finally, we conducted sensitivity analyses specific to ovarian cancer, estimating HRs for douching and talc use combined, and for genital talc use according to reproductive tract patency at the time of use.

Quantitative Bias Analysis

For ever versus never use analyses, we compared four possible scenarios using quantitative bias analysis: (1) no correction; (2) contradictory data correction; (3) contradictory data correction plus categorizing missing or undefined as exposed; and (4) contradictory data correction with multiple imputation of missing or undefined data.

Under no correction, we prioritized reporting at enrollment, categorizing women in the undefined category as nonusers. Women missing both questionnaires were assumed to be missing completely at random. The second scenario added a correction for contradictory data, as described in Appendix 1.

We did this for each of 10 copies of the data, summarizing HRs and 95% CIs using Rubin's rules.[31] Results were consistent across different initiation seeds. For the third scenario, we included the contradictory data correction and categorized all women in the undefined category as users. This contrasted with scenario 2, where the same undefined women were considered never users. Together, scenarios 2 and 3 demonstrate the range of results defined by how women in the undefined category are classified, with the true exposure distribution falling somewhere between the two extremes.

For the fourth scenario, we used multiple imputation with chained equations (MICE; PROC MI, SAS v9.4 [Cary, NC]) to generate covariate-informed probabilistic imputations of the exposure status of participants who were undefined or missing. This scenario should account for covariate-dependent missingness, and we consider it our best estimate of the true association in the absence of recall or other unknown biases. We ran 10 iterations on the data set that already included 10 copies of the data corrected for contradictory responses, then summarized effect estimates across all 100 imputed data sets. We included all the previously described confounders and covariates in the imputation model, as well as each of the cancer outcomes and crude cumulative hazard estimates,[32] which corresponded to the hazard of the earliest of the three cancer events. To ensure that responses regarding ever, frequency, duration, and timing of product use were internally consistent and accounted for coexposure, all talc and douching-related variables were imputed concurrently.

Recall Bias

We additionally investigated the potential impact of recall bias on the association between genital talc use and ovarian cancer. The initial correction and imputation procedures were identical to scenario 4. Additional details are available in the Supplementary Methods, but briefly, we considered (1) recoding a proportion (range 10%-90%) of ovarian cancer cases classified as talc users to be nonusers; (2) recoding a proportion (range 10%-90%) of ovarian cancer cases classified as nonfrequent and short-term talc users to be nonusers; and (3) re-coding a proportion (range 5%-25%) of noncases classified as nontalc users to be infrequent and short-term talc users.

We also generated a single recall bias-corrected estimate that simultaneously corrected cases and noncases. We assumed 25% of ovarian cancer cases initially categorized as infrequent and short-term users were reassigned to be nonusers and 10% of the women without ovarian cancer initially categorized as never users were re-assigned to be infrequent, short-term users. HRs based on this correction are included in the results as examples of plausible, yet cautious, estimates of the association between genital talc use and ovarian cancer after correcting for case-differential recall.

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TABLE 1. Covariate Distributions at Enrollment by History of Genital Talc Use and Douching, Sister Study (2003-2009); n = 50,800

Covariate	Douching			Genital Talc Use		
	Never (n = 29,549) (59%)	Ever (n = 20,542) (41%)	Missing (n = 709)	Never (n = 32,541) (65%)	Ever (n = 17,560) (35%)	Missing (n = 697)
Age, years, mean (SD)	55.6 (9.3)	55.7 (8.5)	53.1 (9.0)	55.6 (9.2)	55.8 (8.6)	53.0 (8.9)
Follow-up time, mean (SD)	12.7 (3.4)	13.5 (2.5)	9.4 (4.8)	12.9 (3.2)	13.2 (2.9)	9.4 (4.9)
Age at menarche, years, mean (SD)	12.7 (1.5)	12.6 (1.5)	12.6 (1.7)	12.7 (1.5)	12.5 (1.5)	12.6 (1.7)
Age at menopause,[a] years, mean (SD)	50.0 (6.1)	49.6 (6.6)	48.2 (7.4)	49.9 (6.2)	49.7 (6.4)	48.1 (7.3)
Baseline BMI (kg/m^2), mean (SD)	27.4 (6.1)	28.3 (6.4)	30.2 (6.7)	27.3 (6.0)	28.8 (6.6)	30.1 (6.6)
Self-reported BMI in 30s, mean (SD)	23.2 (3.8)	23.4 (4.2)	24.4 (4.7)	23.0 (3.8)	23.7 (4.3)	24.5 (4.6)
Self-reported race/ethnicity, No. (%)						
Non-Hispanic White	25,726 (87)	16,399 (80)	361 (51)	27,792 (85)	14,337 (82)	357 (51)
Non-Hispanic Black	1,500 (5)	2,745 (13)	214 (30)	2,115 (7)	2,134 (12)	210 (30)
Hispanic/Latina	1,490 (5)	911 (4)	109 (15)	1,703 (5)	697 (4)	110 (16)
Other	824 (3)	482 (2)	24 (3)	921 (3)	389 (2)	20 (3)
Attained education, No. (%)						
High school equivalent or less	4,138 (14)	3,543 (17)	109 (15)	4,978 (15)	2,708 (15)	104 (15)
Some college	9,179 (31)	7,689 (37)	294 (42)	10,602 (33)	6,267 (36)	293 (42)
Bachelor's degree	8,541 (29)	4,973 (24)	176 (25)	9,016 (28)	4,499 (26)	175 (25)
Graduate degree	7,685 (26)	4,332 (21)	129 (18)	7,937 (24)	4,084 (23)	125 (18)
Census region, No. (%)						
Northeast	5,495 (19)	2,903 (14)	101 (14)	5,154 (16)	3,242 (18)	103 (15)
Midwest	8,162 (28)	5,298 (26)	139 (20)	8,940 (27)	4,522 (26)	137 (20)
South	9,306 (31)	8,033 (39)	348 (49)	10,821 (33)	6,532 (37)	334 (48)
West	6,586 (22)	4,308 (21)	121 (17)	7,626 (23)	3,264 (19)	125 (18)
Ever hormonal birth control use, No. (%)						
Never use	4,919 (17)	2,432 (12)	117 (17)	4,962 (15)	2,395 (14)	111 (16)
Used, 0-5 years	11,673 (40)	8,178 (40)	288 (14)	12,841 (40)	7,016 (40)	282 (41)
Used, >5 years	12,793 (44)	9,828 (48)	297 (42)	14,550 (45)	3,069 (46)	299 (43)
Parity, No. (%)						
No births	5,295 (18)	3,778 (18)	121 (17)	5,797 (18)	3,279 (19)	118 (17)
1 birth	3,900 (13)	3,331 (16)	102 (14)	4,713 (15)	2,521 (14)	99 (14)
2 births	10,822 (37)	7,590 (37)	246 (35)	11,894 (37)	6,514 (37)	250 (36)
≥3 births	9,520 (32)	5,822 (28)	238 (34)	10,119 (31)	5,231 (30)	230 (33)
Menopausal status, No. (%)	19,463 (66)	13,928 (68)	400 (56)	21,353 (66)	12,045 (69)	393 (56)
Hysterectomy, No. (%)	8,622 (29)	7,115 (35)	224 (32)	9,745 (30)	6,001 (34)	215 (31)
Bilateral oophorectomy, No. (%)	5,077 (17)	3,963 (19)	118 (17)	5,613 (17)	3,432 (20)	113 (16)
Tubal ligation, No. (%)	8,004 (27)	6,748 (33)	243 (34)	9,351 (29)	5,399 (31)	245 (35)

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TABLE 1. Covariate Distributions at Enrollment by History of Genital Talc Use and Douching, Sister Study (2003-2009); n = 50,800 (continued)

	Douching			Genital Talc Use		
Covariate	Never (n = 29,549) (59%)	Ever (n = 20,542) (41%)	Missing (n = 709)	Never (n = 32,541) (65%)	Ever (n = 17,560) (35%)	Missing (n = 697)
Patent reproductive tract,[b] No. (%)	15,636 (53)	9,128 (44)	328 (46)	16,581 (51)	8,190 (47)	321 (46)
Hormone therapy use, No (%)						
Never	17,419 (59)	11,222 (55)	500 (71)	18,928 (58)	9,722 (56)	491 (70)
Unopposed estrogen	5,390 (18)	4,530 (22)	121 (17)	6,169 (19)	3,755 (21)	117 (17)
Estrogen plus progestin	6,663 (23)	4,725 (23)	87 (12)	7,364 (23)	4,021 (23)	90 (13)
Smoking, No. (%)						
Never	17,340 (59)	10,780 (53)	391 (55)	18,497 (57)	9,634 (55)	380 (55)
Former	9,985 (34)	7,897 (38)	226 (32)	11,395 (35)	6,489 (37)	224 (32)
Current	2,215 (8)	1,859 (9)	91 (13)	2,641 (8)	1,431 (8)	93 (13)
Alcohol use, No. (%)						
Never or former	5,557 (19)	3,932 (19)	169 (24)	6,074 (19)	3,421 (20)	163 (23)
Current, <7 drinks/week	19,898 (67)	13,832 (67)	466 (66)	21,789 (67)	11,948 (68)	459 (66)
Current, ≥7 drinks/week	4,033 (14)	2,743 (13)	71 (10)	4,610 (14)	2,164 (12)	73 (11)

NOTE. Exclusions: five withdrawals and 79 women diagnosed with breast cancer before completing enrollment. Covariate data were missing as follows (did not use douche [ND], used douche [D], missing douche status [MD], did not use talc [NT], used talc [T], missing talc status [MT]): age at menarche (n = 46 [23 ND, 22 D, one MD; 29 NT, 16 T, one MT]); BMI (n = 17 [12 ND, five D; 10 NT, 7 T]), BMI in 30s (n = 408 [247 ND, 153 D, eight MD; 296 NT, 106 T, six MT]), race/ethnicity (n = 15 [nine ND, five D, one MD; 10 NT, three T, two MT]), attained education (n = 12 [six ND, five ND, one MD; eight NT, two T, two MT]), hormonal birth control use (n = 275 [164 ND, 104 D, seven MD; 188 NT, 80 T, seven MT]), parity (n = 35 [12 ND, 21 D, two MD; 18 NT, 15 T, two MT]), hysterectomy (n = 5 [two ND, three D; three NT, two T]), bilateral oophorectomy (n = 77 [44 ND, 33 D; 47 NT, 30 T]), tubal ligation (n = 16 [12 ND, four D; 13 NT, three T]), patency (n = 1 [one ND; one T]), hormone therapy (n = 143 [77 ND, 65 D, one MD; 80 NT, 62 T, one MT]), smoking (n = 16 [nine ND, six D, one MD; eight NT, six T, two MT]), or alcohol (n = 99 [61 ND, 35 D, three MD; 68 NT, 27 T, four MT]). If baseline and follow-up data are contradictory or the latter is missing, assign status provided at baseline; if missing baseline and not missing follow-up, assign status on the basis of follow-up.

Abbreviation: SD, standard deviation.

[a]Among postmenopausal women.

[b]No hysterectomy and no tubal ligation.

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TABLE 2. Quantitative Bias Analysis of the Association Between Pre-Enrollment Use of Douche or Genital Talc Use and Female Reproductive System–Related Cancers (n = 49,806)

Intimate Care Product Exposure and Cancer Status	Scenario 1: No Corrections, *Assume Unexposed* If Unexposed at Enrollment + Missing at FU, Fill in Missing at Random[a,b]	Scenario 2: Correct Contradictory Data,[c] *Assume Unexposed* If Unexposed at Enrollment + Missing at FU[a]	Scenario 3: Correct Contradictory Data,[c] *Assume Exposed* If Unexposed at Enrollment + Missing at FU[a]	Scenario 4: Correct Contradictory Data[c] + Multiple Imputation[a,d]
Douching				
Cohort exposed, %	41	43	64	53
Premeno breast cancer (n = 613)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.76 (0.63 to 0.91)	0.73 (0.61 to 0.88)	1.18 (0.99 to 1.41)	0.87 (0.71 to 1.06)
Postmeno breast cancer (n = 3,927)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.85 (0.80 to 0.91)	0.84 (0.78 to 0.89)	1.16 (1.08 to 1.24)	0.96 (0.89 to 1.03)
Ovarian cancer (n = 292)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.69 (0.54 to 0.88)	0.67 (0.52 to 0.86)	1.86 (1.41 to 2.45)	1.03 (0.78 to 1.37)
Uterine cancer (n = 433)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.76 (0.62 to 0.93)	0.79 (0.64 to 0.97)	1.11 (0.89 to 1.37)	0.86 (0.68 to 1.08)
Genital talc use				
Cohort exposed, %	35	37	56	40
Premeno breast cancer (n = 613)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.91 (0.76 to 1.10)	0.91 (0.75 to 1.09)	1.36 (1.14 to 1.61)	0.98 (0.81 to 1.19)
Postmeno breast cancer (n = 3,927)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.92 (0.86 to 0.98)	0.92 (0.86 to 0.99)	1.18 (1.11 to 1.26)	0.96 (0.90 to 1.03)
Ovarian cancer (n = 292)				
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	1.07 (0.84 to 1.35)	1.17 (0.92 to 1.49)	3.34 (2.51 to 4.44)	1.82 (1.36 to 2.43)
Uterine cancer (n = 433)				

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TABLE 2. Quantitative Bias Analysis of the Association Between Pre-Enrollment Use of Douche or Genital Talc Use and Female Reproductive System−Related Cancers (n = 49,806) (continued)

Intimate Care Product Exposure and Cancer Status	Scenario 1: No Corrections, *Assume Unexposed* If Unexposed at Enrollment + Missing at FU, Fill in Missing at Random[a,b]	Scenario 2: Correct Contradictory Data,[c] *Assume Unexposed* If Unexposed at Enrollment + Missing at FU[a]	Scenario 3: Correct Contradictory Data,[c] *Assume Exposed* If Unexposed at Enrollment + Missing at FU[a]	Scenario 4: Correct Contradictory Data[c] + Multiple Imputation[a,d]
Never use, HR	1.00	1.00	1.00	1.00
Ever use, HR (95% CI)	0.98 (0.80 to 1.20)	0.98 (0.80 to 1.21)	1.28 (1.04 to 1.58)	1.01 (0.82 to 1.25)

Abbreviations: FU, follow-up; HR, hazard ratio; USD, US dollars.

[a]Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black/African American, Hispanic/Latina, other), attained education (high school equivalent or less, some college, college graduate, graduate degree), examiner-measured BMI at enrollment (continuous, kg/m^2), self-reported BMI age 30-39 years (continuous, kg/m^2), age at menarche (continuous), hormonal birth control use (never, 0-5 years, >5 years), parity (0, 1, 2, ≥3 births), menopausal status (pre or postmenopausal), hormone therapy use (never, unopposed estrogen only, estrogen plus progestin), smoking status (never, former, current), alcohol use (never or former, current <7 drinks/week, current ≥7 drinks/week), and geographic region (Northeast, Midwest, South, West). Women missing one or more of these potential confounders were excluded (n = 994). An additional 8,978 women excluded from the ovarian cancer analysis because of uncertain ovarian cancer status or prebaseline ovarian cancer (n = 225) or prebaseline bilateral oophorectomy (n = 8,753); 15,618 women excluded from uterine cancer analysis because of uncertain uterine cancer status or prebaseline uterine cancer (n = 416) or prebaseline hysterectomy (n = 15,202).

[b]If baseline and follow-up data are contradictory or the latter is missing, assign status provided at baseline; if missing baseline and not missing follow-up, assign status on the basis of follow-up; if missing both time points, randomly assign exposure status on the basis of overall distribution (assumed missing completely at random).

[c]If report unexposed at baseline but exposed at follow-up and age contradictory, assume 80% truly exposed; if report exposed at baseline but never exposed at follow-up, assume 90% of those truly exposed.

[d]Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), weight relative to peers in teen years (lighter, same, heavier, missing), breast cancer (prebaseline/never/incident), ovarian cancer (prebaseline/never/incident), uterine cancer (prebaseline/never/incident), and cumulative hazard values for time to any of the cancer events of interest.
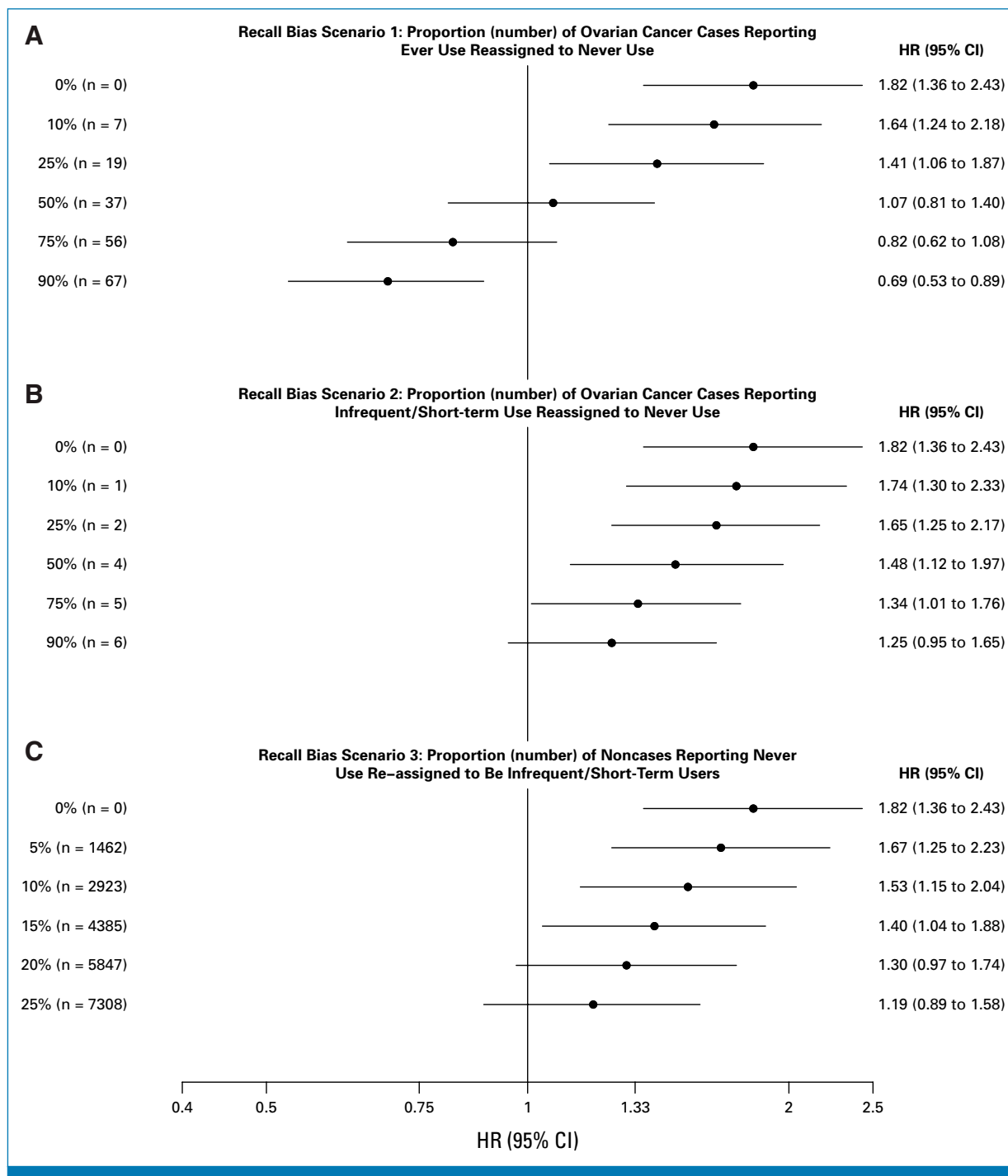
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FIG 2. Forest plots showing covariate-adjusted hazard ratios (HRs) and 95% CIs for the association between ever genital talc use and incident ovarian cancer across different possible scenarios of recall bias induced by exposure misclassification that differed by ovarian cancer status: (A) scenario 1, (B) scenario 2, and (C) scenario 3.

RESULTS

In uncorrected data, 41% of women reported ever douching and 35% reported ever using genital talc before enrollment (Table 1). Compared with women who did not douche, women who douched had higher BMI and were more likely to be non-Hispanic Black, live in the South, have a lower attained education, have had gynecologic surgery, have used unopposed estrogen hormone therapy, and to have smoked. Similarly, genital talc users had higher BMIs than nonusers, and were more likely to be non-Hispanic Black, live in the South, have lower attained education, and have had gynecologic surgery.

The estimated HRs for the uncorrected models where women in the uncertain category (ie, nonusers at enrollment,

TABLE 3. Covariate-Adjusted HR and 95% CIs for the Associations Between Douching and Genital Talc Use by Frequency, Duration, and Timing of Use on the Basis of Models With Contradictory Data Corrections and Multiple Imputation

Intimate Care Product Exposure	% Exp in Full Cohort[a]	Premenopausal Breast Cancer (n = 613)		Postmenopausal Breast Cancer (n = 3,927)		Ovarian Cancer (n = 292) No Recall Bias Correction		Ovarian Cancer (n = 292) Recall Bias Correction[b]		Uterine Cancer (n = 433)	
		% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)
Douching											
Ever v Never use	41/53	44	0.87 (0.71 to 1.06)	53	0.96 (0.89 to 1.03)	56	1.03 (0.78 to 1.36)	—	—	48	0.86 (0.68 to 1.08)
Never use	59/47	56	1.00	47	1.00	44	1.00	—	—	52	1.00
Sometimes use	31/40	38	0.90 (0.73 to 1.10)	38	0.95 (0.87 to 1.02)	35	0.88 (0.65 to 1.21)	—	—	36	0.86 (0.67 to 1.09)
Frequent use	10/14	6	0.69 (0.46 to 1.05)	15	0.98 (0.88 to 1.10)	21	1.50 (1.02 to 2.19)	—	—	12	0.87 (0.60 to 1.26)
			P-trend = .08		P-trend = .48		P-trend = .15		—		P-trend = .29
Never use	59/47	56	1.00	47	1.00	44	1.00	—	—	52	1.00
Short-term use (1 decade only)	17/21	18	0.81 (0.62 to 1.05)	21	0.94 (0.86 to 1.03)	16	0.72 (0.48 to 1.08)	—	—	19	0.80 (0.61 to 1.07)
Long-term use (≥2 decades)	24/32	26	0.93 (0.73 to 1.17)	32	0.96 (0.89 to 1.05)	40	1.27 (0.94 to 1.72)	—	—	29	0.86 (0.65 to 1.13)
			P-trend = .40		P-trend = .40		P-trend = .16				P-trend = .35
Ever v Never use, teens	12/15	16	0.92 (0.72 to 1.18)	12	0.86 (0.78 to 0.96)	12	0.76 (0.50 1.15)	—	—	10	0.73 (0.52 1.03)
Ever v Never use to 20s	31/42	34	0.89 (0.72 to 1.09)	42	0.99 (0.92 to 1.06)	50	1.35 (1.02 to 1.78)	—	—	38	0.89 (0.70 to 1.13)
Ever v Never use, 30s	22/30	24	1.12 (0.90 to 1.41)	31	1.04 (0.96 to 1.13)	39	1.48 (1.11 to 1.99)	—	—	27	0.92 (0.71 to 1.19)
Ever v Never use, year before baseline	14/14	16	1.07 (0.85 to 1.35)	13	1.05 (0.95 to 1.16)	17	1.34 (0.97 to 1.83)	—	—	12	0.98 (0.73 to 1.33)
Genital talc											
Ever v Never use	35/40	36	0.98 (0.81 to 1.19)	40	0.96 (0.90 to 1.03)	55	1.82 (1.36 to 2.43)	54	1.40 (1.04 to 1.89)	42	1.01 (0.82 to 1.25)
Never use	65/60	65	1.00	60	1.00	46	1.00	45	1.00	58	1.00
Sometimes use	17/19	16	0.89 (0.69 to 1.14)	19	0.97 (0.88 to 1.06)	23	1.56 (1.09 to 2.22)	24	1.18 (0.83 to 1.69)	19	0.99 (0.75 to 1.29)
Frequent use	18/20	19	1.10 (0.87 to 1.39)	21	0.96 (0.88 to 1.05)	31	1.99 (1.43 to 2.78)	31	1.81 (1.29 to 2.53)	23	1.03 (0.79 to 1.33)
			P-trend = .68		P-trend = .35		P-trend <.001		P-trend = .001		P-trend = .88
Never use	65/60	65	1.00	60	1.00	46	1.00	45	1.00	58	1.00
Short-term use (1 decade only)	22/23	19	0.91 (0.72 to 1.13)	23	0.93 (0.86 to 1.01)	26	1.48 (1.06 to 2.06)	28	1.17 (0.84 to 1.62)	24	0.98 (0.77 1.26)
Long-term use (≥2 decades)	13/17	16	1.13 (0.87 to 1.47)	17	1.01 (0.92 to 1.11)	27	2.20 (1.52 to 3.19)	27	2.01 (1.39 to 2.91)	18	1.08 (0.80 to 1.45)
			P-trend = .67		P-trend = .76		P-trend <.001		P-trend = .001		P-trend = .76
Ever v Never use, teens	15/15	14	1.06 (0.82 to 1.36)	14	0.95 (0.87 to 1.05)	17	1.17 (0.84 to 1.63)	18	0.98 (0.71 to 1.37)	14	0.92 (0.69 to 1.23)
Ever v Never use, 20s	15/19	16	1.02 (0.79 to 1.31)	18	1.00 (0.92 to 1.10)	31	2.03 (1.49 to 2.77)	31	1.88 (1.37 to 2.57)	18	1.01 (0.77 to 1.33)
Ever v Never use, 30s	11/15	16	1.30 (1.00 to 1.68)	16	1.11 (1.01 to 1.22)	26	2.12 (1.53 to 2.96)	26	2.08 (1.50 to 2.89)	15	1.07 (0.80 to 1.44)

(continued on following page)

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TABLE 3. Covariate-Adjusted HR and 95% CIs for the Associations Between Douching and Genital Talc Use by Frequency, Duration, and Timing of Use on the Basis of Models With Contradictory Data Corrections and Multiple Imputation (continued)

Intimate Care Product Exposure	% Exp in Full Cohort[a]	Premenopausal Breast Cancer (n = 613)		Postmenopausal Breast Cancer (n = 3,927)		Ovarian Cancer (n = 292) *No Recall Bias Correction*		Ovarian Cancer (n = 292) *Recall Bias Correction*[b]		Uterine Cancer (n = 433)	
		% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)	% Exp	HR (95% CI)
Ever *v* Never use, year before baseline	18/18	15	0.87 (0.69 to 1.10)	18	0.92 (0.84 to 1.00)	17	0.91 (0.66 to 1.23)	18	0.83 (0.61 to 1.14)	21	1.09 (0.86 to 1.39)

NOTE. Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black/African American, Hispanic/Latina, other), attained education (high school equivalent or less, some college, college graduate, graduate degree), examiner-measured BMI at enrollment (continuous, kg/m^2), self-reported BMI age 30-39 years (continuous, kg/m^2), age at menarche (continuous), hormonal birth control use (never, 0-5 years, >5 years), parity (0, 1, 2, ≥3 births), menopausal status (pre or postmenopausal), hormone therapy use (never, unopposed estrogen only, estrogen plus progestin), smoking status (never, former, current), alcohol use (never or former, current <7 drinks/week, current ≥7 drinks/week), and geographic region (Northeast, Midwest, South, West). If report unexposed at baseline but exposed at follow-up and age contradictory, assume 80% truly exposed; if report exposed at baseline but never exposed at follow-up, assume 90% are truly exposed. Exposure values imputed if missing both time points or nonuser at baseline and missing follow-up. Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), weight relative to peers in teen years (lighter, same, heavier, missing), geographic region of residence (Northeast, Midwest, South, West, missing), breast cancer (prebaseline/never/incident), ovarian cancer (prebaseline/never/incident), uterine cancer (prebaseline/never/incident), and cumulative hazard values for time to any of the cancer events of interest.

Abbreviations: Exp, exposed; HR, hazard ratio; USD, US dollars.

[a](% before imputation/% after imputation); % of users in comparisons of ever versus never uses, after imputation.

[b]Assume 25% of nonfrequent, short-term users with ovarian cancer misreport their exposure and that 10% of noncases who report no use are actually short-term and infrequent users. Recall bias corrections not made for douching status.

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TABLE 4. Adjusted HRs and 95% CIs Estimating the Association Between History of Douching, Genital Talc Use, and Female Reproductive System–Related Cancers by Subtype (n = 49,806), on the Basis of Multiple Imputation Models With Contradictory Data Corrections

Cancer Type	Cases, No.	Ever Douching, HR (95% CI)	Ever Genital Talc Use, *No Recall Bias Correction,* HR (95% CI)	Ever Genital Talc Use, *Corrected for Recall Bias,*[a] HR (95% CI)
Breast cancer	4,540	0.94 (0.88 to 1.00)	0.96 (0.90 to 1.03)	—
Estrogen receptor–positive	3,272	0.93 (0.86 to 1.01)	0.96 (0.88 to 1.03)	—
Estrogen receptor–negative	574	0.99 (0.82 to 1.21)	1.00 (0.84 to 1.20)	—
Ovarian cancer	292	1.03 (0.78 to 1.36)	1.82 (1.36 to 2.43)	1.40 (1.04 to 1.89)
Medically confirmed	226	0.95 (0.69 to 1.31)	1.89 (1.37 to 2.62)	1.46 (1.06 to 2.02)
Serous	126	1.05 (0.69 to 1.59)	2.12 (1.38 to 3.26)	1.62 (1.06 to 2.48)
Nonserous	100	0.83 (0.52 to 1.34)	1.64 (1.02 to 2.65)	1.29 (0.79 to 2.09)
Uterine cancer	433	0.86 (0.68 to 1.06)	1.01 (0.82 to 1.25)	—
Medically confirmed	338	0.91 (0.70 to 1.17)	1.05 (0.83 to 1.33)	—
Endometrial cancer	317	0.90 (0.68 to 1.17)	1.03 (0.81 to 1.32)	—
Type 1 endometrial cancer	257	0.91 (0.68 to 1.23)	0.99 (0.75 to 1.30)	—
Type 2 endometrial cancer	45	0.80 (0.41 to 1.54)	1.51 (0.77 to 2.95)	—

NOTE. Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black/African American, Hispanic/Latina, other), attained education (high school equivalent or less, some college, college graduate, graduate degree), examiner-measured BMI at enrollment (continuous, kg/m^2), self-reported BMI age 30-39 years (continuous, kg/m^2), age at menarche (continuous), hormonal birth control use (never, 0-5 years, >5 years), parity (0, 1, 2, ≥3 births), menopausal status (pre or postmenopausal), hormone therapy use (never, unopposed estrogen only, estrogen plus progestin), smoking status (never, former, current), alcohol use (never or former, current <7 drinks/week, current ≥7 drinks/week), geographic region (Northeast, Midwest, South, West), and an interaction term for BMI and menopausal status at enrollment. Women missing one or more of these potential confounders were excluded (n = 603). An additional 8,952 women excluded from the ovarian cancer analysis because of prebaseline ovarian cancer or prebaseline oophorectomy; 15,473 women excluded from uterine cancer analysis because of prebaseline uterine cancer or prebaseline hysterectomy. Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), weight relative to peers in teen years (lighter, same, heavier, missing), geographic region (Northeast, Midwest, South, West, missing), breast cancer (prebaseline/never/incident), ovarian cancer (prebaseline/never/incident), uterine cancer (prebaseline/never/incident), and cumulative hazard values for time to any of the cancer events of interest. If report unexposed at baseline but exposed at follow-up and age contradictory, assume 80% truly exposed; if report exposed at baseline but never exposed at follow-up, assume 90% of those truly exposed.
Abbreviations: HR, hazard ratio; USD, US dollars.
[a]Assume 25% of nonfrequent, short-term users with ovarian cancer misreport their exposure and that 10% of noncases who report no use are actually short-term and infrequent users.

missing follow-up) were categorized as nonusers (Table 2, scenario 1) indicated inverse or weakly positive associations between both types of intimate care products and all cancers of interest. Introducing probabilistic corrections for contradictory responses slightly increased exposure prevalence estimates (scenario 2; 43% douching, 37% talc), but HRs were similar to scenario 1. Under the assumption that all women in the uncertain category were users (scenario 3), prevalence estimates were higher (64% douching, 56% talc), and all estimated HRs were >1.00.

After multiple imputation (Table 2, scenario 4), 53% of participants were categorized as ever douchers and 40% were categorized as ever genital talc users. Douching was not strongly associated with any of the examined outcomes. Ever genital talc use was positively associated with ovarian cancer (HR, 1.82 [95% CI, 1.36 to 2.43]), but showed no evidence of

an association with pre- or post-menopausal breast cancer, or uterine cancer.

If ovarian cancer cases overreported their exposure to genital talc, the HR estimates would be biased upward and away from 1.00 (Fig 2, Appendix Table A1). For example, the HR dropped to 1.41 (95% CI, 1.06 to 1.87) if 25% of cases who only reported being exposed on the postdiagnosis questionnaire were truly unexposed. However, the impact of recall bias was greatly reduced when only short-term, infrequent users were reassigned, with HRs indicating a positive association even when 90% were reclassified (HR, 1.25 [95% CI, 0.95 to 1.65]).

If some noncases reporting never exposure were truly users (albeit infrequent and short-term ones), HR estimates would also be biased up and away from the null. However, the

positive association held when we assumed 15% of noncases (HR, 1.40 [95% CI, 1.04 to 1.88]) had misreported. In a model assuming moderate corrections for both cases (reassign 25% of infrequent/short-term users to be nonusers) and non-cases (reassign 10% of nonusers to be infrequent/short-term users), the estimated prevalence of ever talc use changed from 40% (55% in cases) to 45% (54% in cases) and the HR estimate was 1.40 (95% CI, 1.04 to 1.89).

The association between genital talc use and ovarian cancer was higher for frequent (recall bias corrected-HR [HR_{rb}], 1.81 [95% CI, 1.29 to 2.53]) and long-term users (HR_{rb}, 2.01 [95% CI, 1.39 to 2.91]), compared with never users (both *P* for trend = .001; Table 3). Genital talc use during a woman's 20s and 30s was positively associated with incident ovarian cancer, but HRs were near null for teen use. Frequent douching (HR, 1.50 [95% CI, 1.02 to 2.19]) and douching during a woman's 20s (HR, 1.35 [95% CI, 1.02 to 1.78]) and 30s (HR, 1.48 [95% CI, 1.11 to 1.99]) were also positively associated with ovarian cancer.

Results from analyses limited to medically confirmed cancers were similar, and there were no clear subtype differences (Table 4). Estimates based only on exposure status reported at enrollment were mostly null (Appendix Table A2), except for a possible positive association between douching and ovarian cancer. Cancer cases were underrepresented in analyses relying on follow-up data only, and most HRs were <1.0. The exception was ovarian cancer and genital talc use, where an estimated HR of 2.65 (95% CI, 1.91 to 3.70) could indicate some recall bias. Analyses considering person-time accrued since follow-up questionnaire completion were not subject to recall bias, but had reduced sample size; estimates of the genital talc and ovarian cancer association were consistent with a positive association (HR, 1.84 [95% CI, 0.90 to 3.77]).

Analyses jointly considering patency and genital talc use (Appendix Table A3), relative to never use, showed a potentially stronger association with ovarian cancer among women who used while patent (HR, 1.55 [95% CI, 1.14 to 2.09]). Coadjustment did not notably alter estimates (Appendix Table A4).

DISCUSSION

Using newly collected data on intimate care product use in a large cohort of US women, we found evidence supporting a positive association between ever genital talc use and incident ovarian cancer. Frequent douching and douching age 20-39 years were also associated with higher rates of ovarian cancer, but neither genital talc use nor douching was consistently associated with breast or uterine cancer. We did not observe clear differences in HRs by subtypes.

Associations between genital talc use and ovarian cancer remained positive, though attenuated, in most quantitative bias analyses addressing missing data biases and potential differential reporting of genital talc use by ovarian cancer status. In an example scenario correcting for misreporting in both cases and noncases, genital talc use was associated with an approximately 40% higher rate of ovarian cancer, compared with never use, with consistently increasing dose-response patterns for both frequency and duration of use.

These results do not establish causality and do not implicate any specific cancer-inducing agent. Those reporting talc use could be recalling products that contained talc, cornstarch, or a mixture, and women may have used different products at different times. Some talc may have been contaminated with asbestos[5] or other potentially harmful chemicals such as phthalates or parabens.[1,3] Chronic irritation of the ovaries or fallopian tubes from talc or talc-like products could also potentially contribute to carcinogenesis.

Our findings of a positive association between genital talc use and ovarian cancer are consistent with previous studies. Pooled analyses or meta-analyses of case-control studies have produced odds ratios of 1.2-1.4.[33-37] The HR from a pooled analysis of prospective cohort studies[21] also indicated a positive, albeit small association (HR = 1.08), and as previously noted, this effect estimate is likely biased toward the null because of nondifferential misclassification of exposure. This possibility is well illustrated by the Sister Study, where we previously reported 27% ever use of genital talc,[21] but here observe 40% ever use across a wider age range.

Results from the present analysis suggest age 20-39 years may be a window of susceptibility, which is consistent with previous studies that considered ages of use.[38-40] These cover years where hormone levels are high and many women are reproducing. Increased sexual activity during this time period may also correspond to frequent intimate care product use. Additionally, this window occurs before most hysterectomies and tubal ligations are performed, meaning that most women had an intact physical path between application site and the ovaries and fallopian tubes.

Our findings that neither genital talc use nor douching was strongly associated with uterine cancer were consistent with previous literature[24,41,42]; we are unaware of any relevant breast cancer studies. We hypothesized that the endocrine disruptors in douche could affect carcinogenesis for any hormone-related cancer, but only the uterus and ovaries could experience adverse effects caused by direct physical contact. Furthermore, unlike the ovaries and fallopian tube epithelium, uterine epithelium (endometrium) sheds and regenerates frequently via menstruation. This process may flush out the tissue and mitigate talc-induced damage to uterine tissue.

Our exposure assessment included a mix of retrospective and prospective information, integrating some of the strengths and limitations of each data type. Because we only

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considered incident cancers, self-reported intimate care product use at enrollment was not influenced by recall bias. However, the Sister Study's overall scope was wide,[25] and the initial intimate care product questions were limited to two specific periods: age 10-13 years and the last year, and did not capture lifetime exposure or use during the most likely exposure period of age 20-39 years.[8]

The follow-up questionnaire included a more comprehensive assessment, but did so after some individuals had been diagnosed with cancer, allowing for the possibility of recall bias.[22,23] Furthermore, those who died of their disease could not have completed the follow-up questionnaire, allowing for bias because of differential missingness. This was particularly problematic for ovarian cancer, which has a low survival rate.[43]

Because the Sister Study is a volunteer cohort of women who have a sister with breast cancer, participants have higher levels of attained education, are more likely to identify as non-Hispanic White, and have a higher average risk of both breast and ovarian cancers, compared with the general US population. Given that patterns of intimate care product use differ by some of these factors,[2,8] our findings may not generalize to all US women or to international populations. Another important limitation was our sample size. Although the Sister Study is one of the largest studies to collect data on intimate care product use, we lacked statistical power for investigating rare subtypes or differences across subgroups.

Our quantitative bias analyses are a major strength, as they provide a comprehensive illustration of the possible impacts of missing data and recall bias under a variety of scenarios. Although prospectively collected data are preferable for future investigations, our findings demonstrate how retrospective studies can evaluate the possible impact of recall bias. Detailed data on related covariates informed our complex imputations and limited the possibility of residual confounding. However, unmeasured confounding could still be present.

Overall, our findings support the hypothesis that there is a positive association between genital talc use and ovarian cancer incidence, although they do not pinpoint a specific cause or mechanism, and there is still uncertainty as to how much recall bias and missing data could upwardly bias effect estimates. If the underlying biologic mechanisms and causal agents can be confirmed, interventions and policies designed to limit exposure to the harmful components of intimate care products have the potential to reduce ovarian cancer incidence.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

Intimate Care Products and Hormone-Related Cancers

APPENDIX 1. SUPPLEMENTAL METHODS

Patterns of Inconsistency and Missingness in Exposure Data

When comparing responses from enrollment and the fourth detailed follow-up, 68% and 61% of participants provided nonmissing, noncontradictory responses about their ever use of douche and genital talc, respectively (categories 1, 3, 6, and 7; Appendix Table A5). Prioritizing reporting at enrollment, those who initially reported nonuse but later reported using just before enrollment were preliminarily classified as nonusers (category 2; 3% douching, 3% talc), and those initially reporting using but who later reported never use (category 5; 1% douching, 7% talc) were preliminarily considered users. In later models, we included some corrections for these inconsistencies, designed to simultaneously consider that most women reporting use on a questionnaire probably did use at some time point, and that women probably recalled recent use with higher accuracy than past use. As such, we randomly selected 80% of those initially reporting nonuse and later reporting use to be reassigned as ever users, and allowed 90% of those initially reporting use and later reporting nonuse to remain users (reassigning 10%). These corrections were done independent of other covariates.

A small proportion of women missing data from both questionnaires (category 12; 1% douching, 1% talc) remained missing. Women missing intimate care product data from enrollment but not follow-up (categories 9-11; 1% douching, 1% talc) were categorized on the basis of their follow-up response, and those reporting use at enrollment but missing follow-up (category 8; 6% douching, 8% talc) were considered users.

Because the follow-up questionnaire covered a larger age range than the enrollment questionnaire, we did not want to assume that women who initially reported nonuse but did not complete follow-up had never used, especially since women with cancer were overrepresented in this undefined group (douching: 21% overall, 28% of premenopausal breast cancer cases, 24% of postmenopausal breast cancers, 39% of ovarian cancer cases, 24% of uterine cancer cases; genital talc: 19% overall, 27% of premenopausal breast cancer cases, 21% of postmenopausal breast cancers, 37% of ovarian cancer cases, 20% of uterine cancer cases). We implemented a quantitative bias analyses approach to help us compare results after implementing varied approaches to correct or impute exposure for women with conflicting, missing, or undefined status.

Recall Bias Correction

After implementing the MICE-based method described for scenario 4, we implemented recall bias corrections by changing the exposure status of a specified percentage of women with certain characteristics. These were selected at random using the 100-fold augmented data set.

For the first set of recall bias corrections, we recoded a proportion (10%, 25%, 50%, 75%, or 90%) of the ovarian cancer cases to be nonusers if they (1) were nonusers or missing status at enrollment and (2) were categorized as users on the basis of postdiagnostic status or imputation. Because all participants were ovarian cancer–free at enrollment, women who initially reported being users were not considered for reassignment, nor were women who developed ovarian cancer after completing the follow-up questionnaire (n = 30).

For the second set of recall bias corrections, we assumed that ovarian cancer cases who reported being frequent or long-term users were likely reporting their exposure accurately, and therefore, left them unaltered and only changed the exposure status of randomly selected ovarian cancer cases (10%, 25%, 50%, 75%, or 90%) who met the above criteria and had been categorized as infrequent and short-term users.

In a third set of recall bias corrections, we examined the impact of assuming a proportion (5%, 10%, 15%, 20%, and 25%) of noncases categorized as nonusers were truly infrequent, short-term users.

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TABLE A1. Correcting for Recall Bias in the Genital Talc and Ovarian Cancer Association

Recall Bias Correction Model	% Ever Used Genital Talc, Full Cohort (n = 40,829)	% Ever Used Genital Talc, Ovarian Cancer Cases (n = 273)	Ever v Never Genital Talc Use, HR (95% CI)
Cases who ever used genital talc reassigned to be nonusers[a]			
0% reassigned	39	55	1.82 (1.36 to 2.43)
10% reassigned	39	52	1.64 (1.24 to 2.18)
25% reassigned	39	48	1.41 (1.06 to 1.87)
50% reassigned	39	42	1.07 (0.81 to 1.40)
75% reassigned	39	36	0.82 (0.62 to 1.08)
90% reassigned	39	32	0.69 (0.53 to 0.89)
Cases who used genital talc infrequently and for short-term reassigned to be nonusers[b]			
0% reassigned	39	55	1.82 (1.36 to 2.43)
10% reassigned	39	54	1.74 (1.30 to 2.33)
25% reassigned	39	52	1.65 (1.25 to 2.17)
50% reassigned	39	50	1.48 (1.12 to 1.97)
75% reassigned	39	47	1.34 (1.01 to 1.76)
90% reassigned	39	46	1.25 (0.95 to 1.65)
Noncases who never used reassigned to be infrequent, short-term users[c]			
0% reassigned	39	55	1.82 (1.36 to 2.43)
5% reassigned	42	55	1.67 (1.25 to 2.23)
10% reassigned	45	56	1.53 (1.15 to 2.04)
15% reassigned	48	57	1.40 (1.04 to 1.88)
20% reassigned	51	58	1.30 (0.97 to 1.74)
25% reassigned	54	59	1.19 (0.89 to 1.58)
Reassign 25% of infrequent, short-term users with ovarian cancer to be nonusers and 10% of noncase, nonusers to be short-term, infrequent users	45	54	1.40 (1.04 to 1.89)

NOTE. All models also included corrections for contradictory data and multiple imputation for all those missing data on genital talc use as of the fourth detailed follow-up questionnaire, as described previously.

Abbreviation: HR, hazard ratio.

[a]Reassigning x% of participants who met the following criteria to be never users (n ≅ 74): (1) diagnosed with ovarian cancer between enrollment and the fourth detailed follow-up questionnaire; (2) categorized as nonuser of genital talc at enrollment or were missing genital talc data at enrollment; and (3) categorized as ever genital talc user on the basis of the detailed follow-up questionnaire or imputed status.

[b]Reassigning x% of participants who met the following criteria to be never users (n ≅ 7): (1) diagnosed with ovarian cancer between enrollment and the fourth detailed follow-up questionnaire; (2) categorized as nonuser of genital talc at enrollment or were missing talc data at enrollment; (3) categorized as infrequent or short-term genital talc user on the basis of the detailed follow-up questionnaire or imputed status.

[c]Reassigning x% of participants who met the following criteria to be ever users (n ≅ 29,233): (1) not diagnosed with ovarian cancer before the fourth detailed follow-up; (2) categorized as nonuser of genital talc on the basis of follow-up questionnaire or imputed status; (3) categorized as nonuser of genital talc at enrollment or were missing talc data at enrollment.

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TABLE A2. Uncorrected, Adjusted HRs and 95% CIs for the Association Between Intimate Care Products and Hormone-Related Cancers, on the Basis of Use Reported at Enrollment (age 10-13 years or year before enrollment) or on the Fourth Detailed Follow-Up (any use)

Defined by Exposure Status Reported on Enrollment Questionnaire (fully prospective, age 10-13 years and in the 12 months before)			Defined by Exposure Status Reported on Fourth Detailed Follow-Up Questionnaire (mostly retrospective, any use before enrollment, missing excluded)			Defined by Exposure Status Reported on Fourth Detailed Follow-Up (any use before then), and Incident Cases Occurring After That Time (fully prospective)		
Intimate Care Product Exposure and Cancer Status	% Exposed	HR (95% CI), Ever v Never Use		% Exposed	HR (95% CI), Ever v Never Use		% Exposed	HR (95% CI), Ever v Never Use
Douching								
Overall n = 48,618	16		Overall n = 35,725	50		Overall[a] n = 32,891	51	
Premeno breast cancer 596 cases, 48,022 noncases	18	1.06 (0.85 to 1.31)	Premeno breast cancer 385 cases, 35,340 noncases	38	0.84 (0.68 to 1.04)	Premeno breast cancer 20 cases, 1,619 noncases	41	1.07 (0.36 to 3.20)
Postmeno breast cancer 3,852 cases, 44,766 noncases	15	1.04 (0.94 to 1.14)	Postmeno breast cancer 2,747 cases, 32,978 noncases	50	0.94 (0.87 to 1.02)	Postmeno breast cancer 579 cases, 32,214 noncases	51	0.97 (0.82 to 1.15)
Ovarian cancer 286 cases, 39,542 noncases	19	1.30 (0.96 to 1.77)	Ovarian cancer 141 cases, 29,406 noncases	51	0.98 (0.71 to 1.34)	Ovarian cancer 29 cases, 27,189 noncases	50	1.05 (0.51 to 2.16)
Uterine cancer 421 cases, 32,926 noncases	13	0.94 (0.71 to 1.26)	Uterine cancer 297 cases, 24,830 noncases	46	0.87 (0.68 to 1.11)	Uterine cancer 63 cases, 22,605 noncases	48	0.94 (0.55 to 1.61)
Genital talc use								
Overall n = 48,648	27		Overall n = 35,760	31		Overall[a] n = 32,922	32	
Premeno breast cancer 597 cases, 48,051 noncases	24	0.96 (0.79 to 1.17)	Premeno breast cancer 383 cases, 35,377 noncases	29	1.09 (0.87 to 1.36)	Premeno breast cancer 20 cases, 1,618 noncases	30	1.11 (0.39 to 3.14)
Postmeno breast cancer 3,860 cases, 44,788 noncases	27	0.94 (0.88 to 1.01)	Postmeno breast cancer 2,753 cases, 33,007 noncases	31	0.97 (0.89 to 1.05)	Postmeno breast cancer 577 cases, 32,246 noncases	32	1.11 (0.94 to 1.33)
Ovarian cancer 288 cases, 39,570 noncases	28	1.02 (0.79 to 1.33)	Ovarian cancer 140 cases, 29,439 noncases	53	2.65 (1.91 to 3.70)	Ovarian cancer 29 cases, 27,224 noncases	31	1.84 (0.90 to 3.77)
Uterine cancer 422 cases, 32,949 noncases	31	1.08 (0.88 to 1.34)	Uterine cancer 298 cases, 24,856 noncases	34	1.08 (0.85 to 1.38)	Uterine cancer 65 cases, 22,633 noncases	30	0.55 (0.30 to 1.01)

Abbreviation: HR, hazard ratio.

[a]Among women without a breast, ovarian, or uterine cancer diagnosis before they completed the fourth detailed follow-up questionnaire.

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TABLE A3. Adjusted HRs and 95% CIs for the Association Between Genital Talc Use and Ovarian Cancer Accounting for Patency of the Reproductive Tract at Time of Use

Patency and Genital Talc Use	Cases, No.	HR (95% CI) *No Recall Bias Correction*	HR (95% CI) *Corrected for Recall Bias*[a]
Nongenital talc user	133	1.00	1.00
Genital talc user while had patent reproductive tract	148	1.83 (1.36 to 2.46)	1.55 (1.14 to 2.09)
Only used genital talc after hysterectomy or tubal ligation	12	1.70 (0.86 to 3.37)	1.38 (0.69 to 2.75)

NOTE. Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black/African American, Hispanic/Latina, other), attained education (high school equivalent or less, some college, college graduate, graduate degree), examiner-measured BMI at enrollment (continuous, kg/m^2), self-reported BMI age 30-39 years (continuous, kg/m^2), age at menarche (continuous), hormonal birth control use (never, 0-5 years, >5 years), parity (0, 1, 2, ≥3 births), menopausal status (pre- or post-menopausal), hormone therapy use (never, unopposed estrogen only, estrogen plus progestin), smoking status (never, former, current), alcohol use (never or former, current <7 drinks/week, current ≥7 drinks/week), geographic region of residence (Northeast, Midwest, South, West), and an interaction term for BMI and menopausal status at enrollment. Patency defined as having a uterus and open fallopian tubes (ie, no hysterectomy and no tubal ligation); For this analysis, only participants who reported using genital talc reference group is nongenital talc users. Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), and weight relative to peers in teen years (lighter, same, heavier, missing).
Abbreviations: HR, hazard ratio; USD, US dollars.
[a]Assume 25% of nonfrequent, short-term users with ovarian cancer misreport their exposure and that 10% of noncases who report no use are actually short-term and infrequent users.

TABLE A4. Adjusted HRs and 95% CIs for the Association Between Intimate Care Products and Ovarian Cancer, Accounting for Coexposure

Intimate Care Product Use	% Cases (n = 292) Uncorrected/Corrected	HR (95% CI) *No Recall Bias Correction*	HR (95% CI) *Corrected for Recall Bias*[a]
Nonuser	24/24	1.00	1.00
Genital talc user, douche nonuser	20/20	1.85 (1.23 to 2.77)	1.38 (0.90 to 2.13)
Douche user, nongenital talc user	21/22	0.95 (0.63 to 1.43)	0.97 (0.64 to 1.48)
Used both douche and genital talc	35/34	1.73 (1.19 to 2.52)	1.39 (0.95 to 2.02)
Ever *v* never douching, adjusting for genital talc use	56/56	0.94 (0.71 to 1.25)	0.99 (0.75 to 1.31)
Ever *v* never genital talc use, adjusting for ever douching	55/54	1.84 (1.37 to 2.46)	1.40 (1.04 to 1.90)

NOTE. Correlation between douching and genital talc use: Pearson r^2 = 0.18 (uncorrected), Pearson r^2 = 0.16 (corrected). Adjusted for race/ethnicity (non-Hispanic White, non-Hispanic Black/African American, Hispanic/Latina, other), attained education (high school equivalent or less, some college, college graduate, graduate degree), examiner-measured BMI at enrollment (continuous, kg/m^2), self-reported BMI age 30-39 years (continuous, kg/m^2), age at menarche (continuous), hormonal birth control use (never, 0-5 years, >5 years), parity (0, 1, 2, ≥3 births), menopausal status (pre or postmenopausal), hormone therapy use (never, unopposed estrogen only, estrogen plus progestin), smoking status (never, former, current), alcohol use (never or former, current <7 drinks/week, current ≥7 drinks/week), geographic region of residence (Northeast, Midwest, South, West), and an interaction term for BMI and menopausal status at enrollment. Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), and weight relative to peers in teen years (lighter, same, heavier, missing).
Abbreviations: HR, hazard ratio; USD, US dollars.
[a]Assume 25% of nonfrequent, short-term users with ovarian cancer misreport their exposure and that 10% of noncases who report no use are actually short-term and infrequent users.

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TABLE A5. Assigning of Exposure Status as of Enrollment (use in the 12 months before), According to Data Collected at Enrollment (2003-2009) and Detailed Follow-Up 4 (2018-2019)

Category / Intimate Care Product Use Status	% Participants in Category, Douching — Overall	% Participants in Category, Douching — Cases (premeno breast/postmeno breast/ovarian/uterine)	% Participants in Category, Genital Talc — Overall	% Participants in Category, Genital Talc — Cases (premeno breast/postmeno breast/ovarian/uterine)	Quantitative Bias Analysis 0 = Unexposed, 1 = Exposed — Scenario 1: No Corrections, Fill in Missing[a,b]	Scenario 2: Fill in Missing,[a,b] Correct Contradictory Data,[c] *Extreme Unexposed*	Scenario 3: Fill in Missing,[b] Correct Contradictory Data,[c] If Undefined (unexposed at enrollment, but missing follow-up) Assume Exposed *Extreme Exposed*	Scenario 4: Correct Contradictory Data,[c] Use Multiple Imputation to Fill in Missing or Undefined[d]
1. Nonuser at both time points	34	37/32/23/35	41	40/40/20/38	0	0	0	0
2. Nonuser at enrollment, later said used at enrollment *Eligible for correction*	3	2/2/2/4	3	2/3/5/3	0	Randomly select 80% to be exposed	Randomly select 80% to be exposed	Randomly select 80% to be exposed
3. Nonuser at enrollment, later said used with age reports not contradictory	25	12/25/16/21	8	6/8/9/6	1	1	1	1
4. Nonuser at enrollment, missing at follow-up *Eligible for imputation*	21	28/24/39/24	19	27/21/37/20	0	0	1	Multiply impute
5. User at enrollment, never user at follow-up *Eligible for correction*	1	1/1/0/2	7	3/7/2/7	1	Randomly select 10% to be unexposed	Randomly select 10% to be unexposed	Randomly select 10% to be unexposed
6. User at enrollment and follow-up. Consistent ages	5	6/4/4/3	8	8/7/6/9	1	1	1	1
7. User at enrollment and follow-up but ages somewhat inconsistent	4	3/4/2/3	4	2/4/5/5	1	1	1	1
8. User at enrollment, missing follow-up	6	8/5/13/6	8	9/9/15/10	1	1	1	1
9. Missing enrollment, never user at follow-up	0	0/0/0/0	1	1/0/0/0	0	0	0	0
10. Missing enrollment, used at age other than enrollment at follow-up	0	0/0/0/0	0	0/0/0/0	1	1	1	1
11. Missing enrollment, used at enrollment according to follow-up	0	0/0/1/1	0	0/0/0/0	1	1	1	1
12. Missing all	1	2/1/1/2	1	2/1/1/2	Assume 41% used douche, 35% used genital talc	Assume 41% used douche, 35% used genital talc	Assume 41% used douche, 35% used genital talc	Multiply impute

Abbreviation: USD, US dollars

[a]If enrollment and follow-up data are contradictory or the latter is missing, use status provided at enrollment.

[b]Assumes all those missing douching or genital talc data from both time points are missing completely at random (ie, without respect to disease status or other factors), and randomly impute 41% exposed to douching and 35% exposed to genital talc.

[c]If report unexposed at enrollment but exposed at follow-up and age contradictory, assume 80% truly exposed; if report exposed at enrollment but never exposed at follow-up, assume 90% of those truly exposed.

[d]Multiple imputation models included covariates considered confounders for the multivariable analysis in addition to childhood household income level (well off, middle income, low income, poor, missing), adult household income (<$50,000 USD/year, $50-99,999 USD/year, ≥$100,000 USD/year), highest attained education level of the head of the household when the participant was age 13 years (<high school, high school or equivalent, some college, college graduate, missing), marital status (never married, divorced/widowed/separated, married/living as married, missing), weight relative to peers in teen years (lighter, same, heavier, missing), breast cancer (prebaseline/never/incident), ovarian cancer (prebaseline/never/incident), uterine cancer (prebaseline/never/incident), and cumulative hazard values for time to any of the cancer events of interest.